LA-UR-15-24382
Approved for public release; distribution is unlimited.

Title:	Longer-lived Diagnostic Isotopes: The 44Ti/44Sc Radionuclide Generator for Positron Emission Tomography (PET).
Author(s):	Radchenko, Valery
Intended for:	National Isotope Development Center Newsletter
Issued:	2015-06-11 (Draft)

Longer-lived Diagnostic Isotopes: The $^{44}Ti/^{44}Sc$ Radionuclide Generator for Positron Emission Tomography (PET).

Radionuclide generator systems find broad application in clinics largely due to their cost effectiveness and independence from accelerator or nuclear reactor facilities [1]. A radionuclide generator can be "milked" or eluted on a regular basis to provide diagnostic or therapeutic radionuclides on site and when needed.

During the last decade, with improvement of PET imaging technologies, several generator systems are of growing interest among researchers and clinicians. One notable example is the $^{68}Ge/^{68}Ga$ system, which provides ^{68}Ga ($t_{1/2}$ 67.6 min, 88.9% β^+ branching ratio, $E_{mean\ \beta+}$ = 0.83 MeV) that can be attached to targeting biomolecules via bifunctional chelating agents. This isotope is of great interest for the imaging [2] of cancer and infection. In the case of $^{68}Ge/^{68}Ga$, the parent radionuclide ^{68}Ge ($t_{1/2}$ = 270.8 d) has been produced at the Los Alamos National Laboratory (LANL) and the Brookhaven National Laboratory (BNL) on a routine basis.

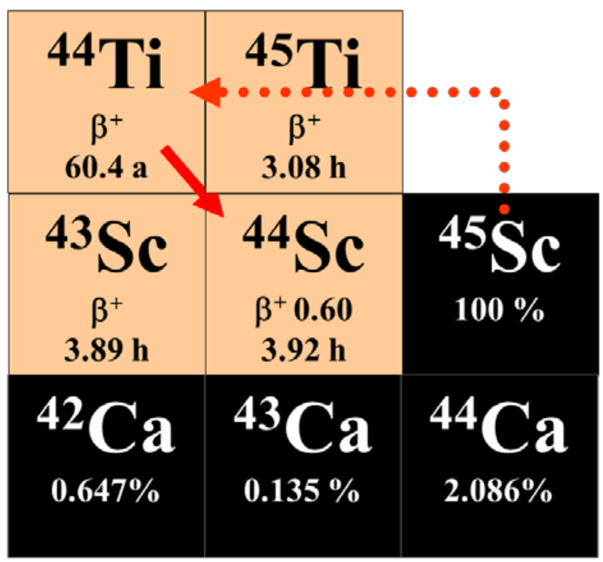

Figure 1. Production and decay pathway for the generator system $^{44}Ti/^{44}Sc$.

Another generator system proposed for imaging purposes is the $^{44}Ti/^{44}Sc$ pair (Fig. 1), in order to make available the PET isotope ^{44}Sc ($t_{1/2}$ 3.97 h, 94.27 % β^+ branching ratio, $E_{<\beta+>}$ = 0.63 MeV). While this system is similar to $^{68}Ge/^{68}Ga$, it exhibits salient differences. In particular, scandium-44's half-life is almost four times the half-life of ^{68}Ga. The longer half-life enables the tracking of slower biological processes and also allows for more complex radiopharmaceutical preparations post-elution. Scandium-44's parent, ^{44}Ti, has a half-life of roughly 60 years, opening up the possibility for a long-term daughter radionuclide source. Such a long half-life, however, also creates economic and engineering challenges because of the large quantity of long-lived ^{44}Ti that must be secured on the generator column. High ^{44}Ti activities also require high particle beam currents and long irradiation times. Investigators of Los Alamos National Laboratory and Brookhaven National Laboratory are currently looking into the production of parent ^{44}Ti at quantities that could make pre-clinical and clinical evaluations of ^{44}Sc as a PET agent possible. Two proton beam irradiations of natural scandium metal targets were performed at the Isotope Production Facility (IPF) at LANL during the run cycle 2014-2015 at lower proton energies ("C-slot" target position). These irradiations resulted in the combined formation of more than 10 mCi (~400 MBq) of ^{44}Ti, a significant amount compared to current world-wide stocks of this rare radioisotope (Fig. 2). In parallel, the

Brookhaven team has been working on both design and fabrication of additional proton beam targets for the future bulk manufacturing of ^{44}Ti activity.

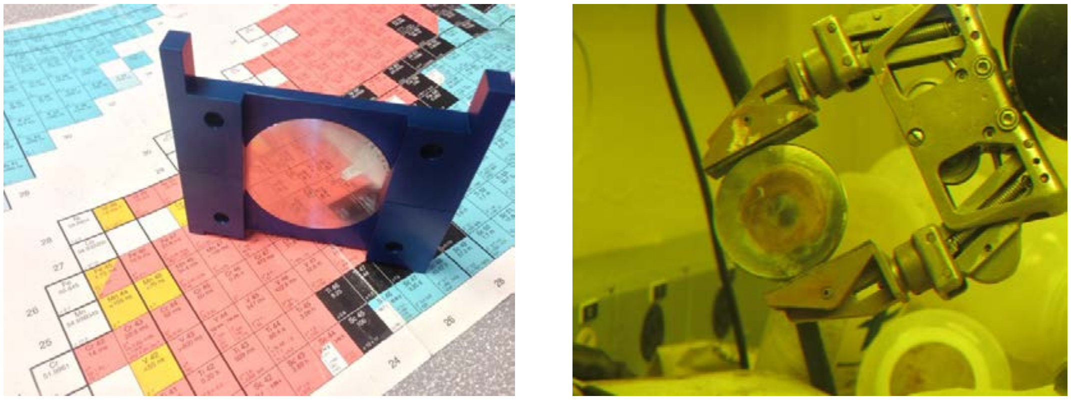

Figure 2. Scandium target before (left) and after proton irradiation at LANL (right)

After irradiation, accumulated ^{44}Ti needs to be recovered chemically from the scandium target. For this pupose, the first target (containing ~ 5 mCi of ^{44}Ti) was utilized for the development of chemical separation methods to isolate microgram quantities of ^{44}Ti from many gram amounts of natural scandium. Based on recent experiments conducted by radiochemists at LANL and BNL, ion exchange column chromatography seems to be the most elegant and efficient strategy to attain this goal, and optimization of the chemical separation is currently underway.

After isolation and purification from byproduct radionulides, long-lived ^{44}Ti will be fixed to a solid support for the repeated elution of daughter nuclide ^{44}Sc. Different extraction systems are under consideration to ensure long-term sorption of ^{44}Ti and near-quantitative recovery of the in-grown ^{44}Sc imaging isotope. Prototype sorption systems are slated for elution performance and ^{44}Ti breakthrough evaluation, the two main parameters detemining the quality of a radionuclide generator design. Once a successful system has been found and demonstrated, test generators are expected to be available for ^{44}Sc labeling and biological studies.

References:

1. *F. Rösch, F. F. Knapp Jr. Radionuclide Generators Handbook of Nuclear Chemistry, Springer 2011, pp 1935-1976.*
2. *F. Rösch, Past, present and future of ^{68}Ge/^{68}Ga generators. Appl. Radiat. Isot. 2013 76,24-30.*